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THROMBOSIS

The problem of thrombosis has attracted far too little attention from physicians in proportion to its importance. We are daily confronted with the disastrous consequences of this phenomenon and its chameleon manifestations. As Edgar Allen suggested, it is challenging to contemplate the effect which would be produced on morbidity and mortality rates among the aging by the reduction of the tendency of the blood toward thrombosis by one third or more.

The complex process of thrombosis is not completely understood, but certain important factors can be outlined briefly. Several mechanisms operate simultaneously and interdependently. There are differences of opinion on numerous points but the following is considered to be the general scheme of the chemical aspect of the process. Thrombokinase is believed to be a lipoprotein closely allied to cephalin. It is found in all tissues, the lungs, platelets, and brain being its richest sources. It is released especially following trauma. In combination with calcium it is believed to constitute a proteolytic enzyme analagous to trypsin which reacts with prothrombin to form thrombin. Prothrombin is probably a protein which is found closely associated with the plasma globulin and is normally present in a concentration of approximately 40 mg. per cent. It is not absolutely certain whether the conversion of prothrombin to thrombin by thrombokinase plus ionic calcium is on a strictly quantitative basis or whether the effect is in reality on the velocity of conversion alone. Thrombin, a protein is probably a hydrolysis product of prothrombin. It is believed to be the proteolytic enzyme producing the next step in this process, namely, the splitting of fibrinogen into fibrin and serum globulin. Thrombin is capable of converting 2000 times its weight of fibrinogen into fibrin. Other proteolytic enzymes such as papain, and numerous snake venoms may replace thrombin experimentally to produce this conversion. No apparent stoichiometric relationship exists between thrombin and fibrinogen.

Fibrinogen is a globulin type protein of certain special solubilities. It is produced exclusively in the liver. Except in very severe forms of liver disease, the fibrinogen concentration of the blood is maintained at a normal level of 0.2 to 0.4 mg. per cent. Its conversion from the physical state of a disperse hydrosol to a quasi crystalline fibrin gel is the sine qua non of natural blood clotting.

Calcium was formerly thought to be capable of producing the change from prothrombin to thrombin alone but Mellanby demonstrated that this conversion is actually effected by thrombokinase in the presence of calcium ions as mentioned above. Although some delay in the formation of the clot may occur in its absence, calcium is not necessary for coagulation once thrombin has been fully elaborated. (There is one brief period in the conversion process when the removal of calcium causes inactivation of the thrombin.)

The above factors represent the action of the chemical coagulants in the blood. There are natural anti-coagulants which by acting in proper balance prevent the blood from clotting under normal conditions. Of these we know the most about heparin, although it is present only in minute quantities in the circulating blood and is not per se responsible for the maintenance of the fluidity of the blood in the living body. The total effect of the unknown anticoagulants may very well be greater than that of the heparin found in the normal blood.

Heparin is a strongly acidic compound containing mucoitin polysulfuric acid, acetic acid, and glycuronic acid plus a base glucosamine. It arises in the mast cells of Ehrlich which are found chiefly in the vicinity of the finer blood vessels. These cells are especially concentrated in the capsule of the liver, the lung and the subcutaneous tissues. Histologically, heparin inclusions may be detected in the mast cells by the characteristic metachromatic stain which they yield with toluidine blue. Jorpes suggests that the mast cells may well be considered a hormonal system feeding heparin into the blood and in this the present author concurs.

Heparin acts as an anti-coagulant in at least two ways. First, it retards the rate of conversion of prothrombin to thrombin to an extent which is inversely proportional to the amount of thrombokinase present. Second, there is an anti-effect on the amount (effectiveness)of the thrombin formed. It is thought that heparin is only active naturally in the presence of at least one normal plasma antithrombin-part of the albumin fraction.

Thus heparin (plus the other anti-coagulants) and thrombokinase are direct antagonists,—coagulation being prevented unless thrombokinase is predominant. The release of additional thrombokinase following cellular injury of any kind, *including surgery* may tilt the scales toward thrombosis.

Other factors also play a role in the actual production of a clot. It has been shown that under favorable conditions blood may be kept stagnant between two ligatures applied to a vein without clotting *if the internal lining of the vessel is unaltered and intact.* Some roughness of the internal lining either due to injury, an arteriosclerotic plac, or minute nodules such as those described by Dietrich following infection, appears to be usually necessary to provide an anchorage to which the thrombus may affix itself in the presence of stagnation and other favorable conditions.

To this anchorage, aided by the sticky fibrin referred to above, cellular elements adhere. Commonly, but not always, the first elements to collect are the platelets, and white cells. These form what is known as the white "head" of the thrombus which is usually firmly fixed to the vessel wall. As the process continues all blood elements become involved, the clot enlarges and the red "tail" attached to the white "head" extends along the lumen of the vessel, usually moving free in the surrounding blood. In small vessels the white head is frequently large in proportion to the rest of the clot. In large vessels it may be so small as to be almost invisible, the red

"tail" making up most of the thrombus.

An attempt has been made to outline briefly the interplay of various known factors which contribute to the process of thrombosis. We should constantly reiterate that *the known* constitutes only a small fraction of the total facts in this field, and discipline our thought accordingly.

It is obviously impossible to herein describe all of the effects of thrombosis in man and a treatment for each. An attempt will be made, therefore, to outline some general concepts of the pathological physiology produced and some therapeutic suggestions aimed at interrupting the process or aiding a restoration toward normal.

Thrombosis may occur in either an artery or a vein and may produce an almost unlimited variety of secondary effects. A thrombus one fourth of an inch long which forms in certain sites in a cerebral or coronary artery may produce paralysis, chronic invalidism, or death, whereas, by contrast we see thrombi many inches long in the veins of the legs producing only discomfort and perhaps edema. Thrombosis is precipitated by many factors capable of producing trauma, inflammation, stagnation, narrowing of a lumen, irregularity of a vessel wall or changes in the balance in the blood in favor of thrombokinase. A partial list includes — Arterio or phlebosclerosis, surgical or other mechanical injuries, pregnancy, malignancy, local suppurative processes, e.g. mastoid with jugular vein thrombosis; blood dyscrasias, e.g. polycythemia vera and the leukemias; infectious diseases, e.g. pneumonia and typhoid fever; vascular diseases, e.g. thromboangiitis-obliterans, periarteritis nodosa, and thrombo-phlebitis migrans.

If the blockage produced is in an artery the effect is primarily ischemia with its secondary reactions. If the blockage is venous we have the complex results of venous stasis with edema and later frequently a relative ischemia. In either instance the total effect on the tissues supplied or drained by the vessel affected may be markedly modified by the total collateral circulation available to the same area.

Each specific situation, be it pregnancy, mastoiditis, polycythemia or coronary thrombosis has its own recognized therapeutic indications. These must of necessity be followed.

Recently certain agents have become available which have made possible further studies in experimental therapeutics in this field. The first of these was purified Heparin which could be administered intravenously. The action of this substance, namely to counterbalance thrombokinase, has been explained above. It has been demonstrated by many workers that the *judicious* and *well-controlled* use of this substance will result in the abortion of the thrombotic process in most instances of thrombophlebitis. It is invaluable in vascular surgery to prevent the most frequent and serious complication—thrombosis at the site of the incision of the vessel wall. It has also been used with success in the treatment of thrombosis of the central retinal vein. It is highly probable that heparin does not dissolve clots already formed but may prevent the further propagation of them. This is frequently the difference between life and death, so must not be under-estimated. It has also been used as a prophylactic against postoperative thrombosis. Crafoord reported that of 325 cases heparinized postoperatively there were no thrombi, whereas, in a control group of 302 non-heparinized patients 33 thrombotic complications occurred with 18 certain pulmonary emboli and 9 deaths with postmortem proof.

The value of this principle of treatment and prevention was thus established, but heparin has not been widely used for the following reasons:

1. It is difficult to administer, requiring either continuous intravenous infusions or 4 or 5 injections a day for from 5-20 days.

2. Unless controlled by frequent checks of the clotting time, it is potentially dangerous, and deaths have been attributed to its use.

3. It is difficult to prepare in large quantities and hence is very expensive. The cost may run to between $15 and $30 a day.

4. There have been a number of therapeutic failures.

Recently due to the outstanding work of Link and his co-workers the active agent which produces hemorrhagic sweet clover disease in cattle has been isolated and synthesized. It is 3,3′ Methylene-Bis (4-Hydroxycoumarin) and is known as Dicumarol (formerly Dicoumarin). This substance diminishes the clotting tendency of the blood. The most significant change in the blood is found in the marked prolongation of the prothrombin time. The prothrombin mechanism is apparently interfered with and the action of the substance is controlled by careful daily checking of the prothrombin time. It, like heparin may produce serious hemorrhages, but if carefully controlled appears safer for general use. Its action may be terminated at any time by the use of one or two *fresh blood* transfusions. Curiously Vitamin K in therapeutic doses does not affect the action of Dicumarol. It has the advantages of ease of administration, e.g. one—300-mg. capsule daily or less often depending on the prothrombin times which should be prolonged about one half (e.g. 22 seconds to 30-35 seconds*). It is also inexpensive and can be prepared in large amounts. Thus far its use has been confined to experimental studies. It has been successfully used in the treatment of thrombophlebitis, in the postoperative prevention of thromboses, and in the treatment of patients who have already had one pulmonary embolism. Its value in many other conditions, including other thrombosing peripheral vascular diseases, coronary thrombosis and additional unexplored fields remains to be determined. For details regarding these substances the reader is referred to the references appended. More than 150 compounds related to Dicumarol have been isolated. These new substances should be regarded as being of the greatest potential experimental interest with their possible therapeutic value yet to be established. A new and illuminating chapter on the understanding and treatment of thrombosis is being written by the combined efforts of many workers. It is safe to predict at this point that it will be of great significance.

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